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# Esophageal Mucoepidermoid Carcinoma Containing Signet-Ring Cells: Three Case Reports and a Literature Review

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We report 3 cases of esophageal signet-ring cell carcinoma which were found in a set of 505 resected esophageal tumors. The incidence of esophageal signet-ring cell carcinoma was 0.6%. All of the signet-ring cell carcinomas were histologically mixed with squamous cell carcinoma (mucoepidermoid carcinoma). The signet-ring cells had intracellular mucin, which was positive for both periodic acid-Schiff (PAS) and alcian blue at pH 2.5. At the time of presentation, extensive extraesophageal tumor spread and local extension were found in all cases. All of the patients died within 2 years after the esophagectomy irrespective of whether they received chemotherapy or radiotherapy. Our results, and those previously reported, suggest that most esophageal carcinomas containing signet-ring cell carcinoma are aggressive neoplasms associated with a poor prognosis after esophagectomy. *J. Surg. Oncol. 1999;71:54–57.* © 1999 Wiley-Liss, Inc.

KEY WORDS: **esophageal neoplasm; pathology; signet-ring cell carcinoma; mucoepidermoid carcinoma**

## INTRODUCTION

Esophageal mucoepidermoid carcinoma is defined as a tumor that is characterized by an intimate mixture of squamous cells, mucus-secreting cells, and cells of an intermediate type [1]. Esophageal mucoepidermoid carcinoma is a rare esophageal tumor and is believed to arise from the esophageal glands [1,2]. The incidence of esophageal mucoepidermoid carcinoma is estimated to range from 0.7% to 2.2% for all esophageal malignancies [3–5]. Additionally, mucoepidermoid carcinoma of the esophagus which contains signet-ring cells is extremely rare [6–8]. The biological behavior of these tumors is poorly understood. In order to clarify the clinicopathologic characteristics of esophageal mucoepidermoid carcinoma containing signet-ring cells, we have reviewed our surgical pathology records, which consist of 505 cases of esophageal cancers diagnosed between 1982 and 1996. In this set, we found 3 cases of this tumor (0.6%). In this report, we describe the clinicopathologic features of the 3 cases, and we discuss the possible histogenesis and clinical implications of these tumors.



## CASE REPORTS

### Case 1

In June 1988, a 69-year-old man was admitted to the First Department of Surgery, Niigata University Hospital, complaining chiefly of dysphagia and upper abdominal pain of 4 months' standing. A barium swallow on admission revealed a constricting tumor measuring 9.5 cm in length in the lower third of the esophagus. Biopsy specimens taken from the tumor during an endoscopy showed poorly differentiated squamous cell carcinoma of the esophagus. Because a computed tomographic (CT) scan showed a direct involvement of the right atrium by the tumor, in addition to multiple metastases to the paratracheal lymph nodes, radiotherapy (20 Gy) was performed prior to surgery. A transthoracic esophagectomy with left cervical, mediastinal, and abdominal lymphadenectomies was carried out in October 1988. The patient

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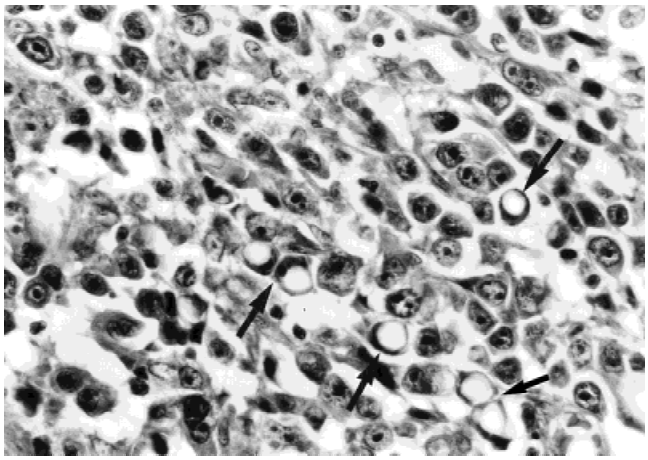

Fig. 1. Histologic appearances of the signet-ring cells (arrows) mixed with poorly differentiated squamous cell carcinoma (case 1). Hematoxylin-eosin; ×80.

died of pneumonia 7 months after the operation with no evidence of tumor recurrence.

**Pathology.** The resected specimen showed a diffusely infiltrative tumor. It measured 6.3 cm in length with a shallow ulceration located in the mid and lower esophagus. Histologically, the tumor was a poorly differentiated squamous cell carcinoma penetrating the esophageal wall. Most parts of the tumor were located in the subepithelial layers of the esophagus. Some of the tumor cells showed the same morphologic features as those of signet-ring cell carcinomas of the stomach or colon (Fig. 1). These signet-ring cells showed intracellular mucin, which was positive for both periodic acid-Schiff (PAS) and alcian blue at pH 2.5. The signet-ring cells were intimately mixed with the squamous carcinoma cells. Marked vessel invasion was present in the subepithelial layers around the tumor. Metastatic deposits were found in 1 of the perigastric lymph nodes.

## Case 2

In March 1989, a 61-year-old man was admitted to our hospital complaining chiefly of a sore throat and pain in swallowing of 9 months' standing. A barium swallow and an endoscopy revealed an ulcerative tumor in the upper third of the esophagus. Biopsy specimens taken from the tumor showed poorly differentiated squamous cell carcinoma. A preoperative CT scan demonstrated tumor invasion to the thyroid gland and left cervical lymphadenopathy. Bronchoscopy showed left vocal cord palsy and a bulging of the tracheal membranous portion due to tumor compression. A laryngopharyngo-total-esophagectomy with bilateral cervical, mediastinal, and abdominal lymphadenectomies was performed in April 1989. Although the patient's postoperative course was uneventful, he died 4 months after the operation of extensive tumor recurrence in the bilateral neck and mediastinum.

Fig. 2. Gross appearance of the esophagectomy specimen (case 2), showing an ulcerated tumor in the cervical esophagus (arrow).

**Pathology.** The resected specimen showed an ulcerative tumor located in the cervical esophagus (Fig. 2). Microscopically, the tumor was shown to be a poorly differentiated squamous cell carcinoma intermingled with signet-ring cell carcinoma (Fig. 3). The tumor cells were diffusely infiltrated and spread in the submucosal layers from the cervical esophagus proximally to the hypopharynx and distally to the lower esophagus. The tu-

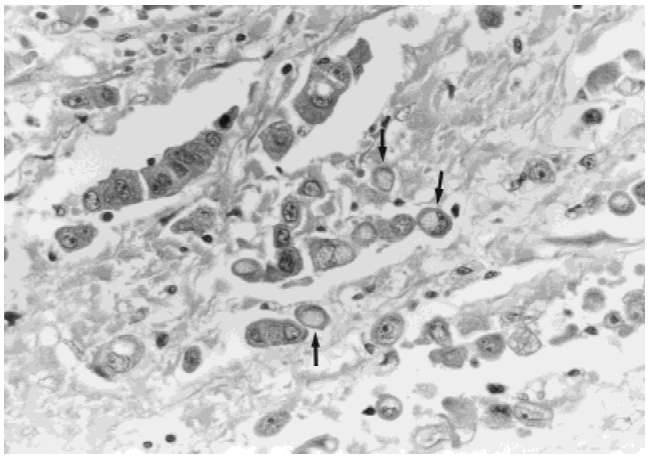

Fig. 3. Histologic features of the signet-ring cell carcinoma component (case 2). Arrows indicate the signet-ring cells intermingled with squamous carcinoma cells. Hematoxylin-eosin; ×120.

Fig. 4. Diffuse subepithelial infiltration of tumor cells in the esophageal wall (case 2). Hematoxylin-eosin; ×6.

mor was 19.8 cm long (Fig. 4). Carcinoma in situ was found at the tumor margin exposed to the esophageal lumen. The thyroid gland resected together with the larynx was involved by the tumor cells. The tumor metastasized extensively to the lymph nodes of the bilateral neck and upper mediastinum.

### Case 3

In October 1993, a 56-year-old man was admitted to our hospital complaining chiefly of upper abdominal pain of 6 months' standing. A physical examination on admission revealed a left supraclavicular lymphadenopathy, measuring 4.0 cm in diameter (Virchow metastasis). A barium swallow revealed a constricting lesion measuring 13 cm long in the lower third of the esophagus. The biopsy specimens taken from the esophageal tumor showed well-differentiated squamous cell carcinoma. A preoperative CT scan showed apparent metastases to the left supraclavicular and abdominal paraaortic lymph nodes in addition to extensive metastases to the mediastinal lymph nodes. A palliative transhiatal esophagectomy was performed after 3 courses of neoadjuvant chemotherapy, which consisted of cisplatin, 5-fluorouracil, and leucovorin. The patient received 2 additional courses of the same chemotherapy postoperatively. Although the lymph node metastatic diseases temporarily responded to the chemotherapy, tumor recurrence became evident in the lung, bone, and lymph nodes of the mediastinum and abdomen. The patient died of recurrent disease 22 months after the esophagectomy.

**Pathology.** The esophagectomy specimen showed a thickening of the esophageal wall in the mid and lower esophagus, with most of the tumor covered by normal squamous epithelia. Histologically, the esophageal tumor showed a poorly differentiated squamous cell carcinoma infiltrating down to the adventitia through the muscularis propria. A mixture of squamous cells and tumor cells with intracellular mucin secretion was found in the tumor tissue, particularly in the lamina propria mucosae and submucosa. Intracellular mucin was detected by both PAS (Fig. 5) and alcian blue at pH 2.5. A marked vascular invasion and intramural metastases were found around the esophageal tumor. Metastatic deposits were present in some of the mediastinal and abdominal lymph nodes which were simultaneously resected.

## DISCUSSION

Recent studies have shown that glandular or mucin-secreting components are not rarely found in squamous cell carcinomas of the esophagus [9]. However, mucoepidermoid carcinoma containing signet-ring cell carcinoma identical to that of the stomach or colon is extremely rare in the esophagus. To the best of our knowledge, only 3 cases of such tumors have been reported so far [6–8]. Nezu et al. [8] found only 1 case of this tumor (0.09%) in their series, which consisted of 1,128 patients with esophageal carcinoma. We found 3 cases (0.6%) of mucoepidermoid carcinoma containing signet-ring cells in 505 esophagectomy specimens with esophageal cancer.

Formerly, esophageal mucoepidermoid carcinoma was thought to be a less aggressive tumor than squamous cell carcinoma, as is true in mucoepidermoid carcinoma of the salivary glands. However, recent studies have reported that esophageal mucoepidermoid carcinoma has a very aggressive nature and is associated with a poor prognosis after esophageal resection [3,7]. The prognosis after esophagectomy also seems to be dismal in cases of esophageal carcinoma with signet-ring cells. Extensive local extension and extraesophageal spread were present at the time of surgery or after esophageal resection in all of our 3 cases and in 2 of the 3 cases previously described [6,7]. Furthermore, complete tumor removal could be

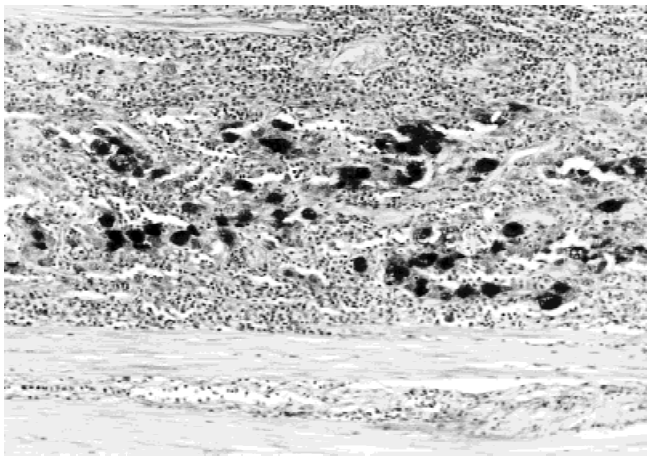

Fig. 5. Intracellular mucin positive for both periodic acid-Schiff (PAS) and alcian blue at pH 2.5 in the signet-ring carcinoma component (case 3). PAS; ×40.

performed in only half of these cases. None of the patients in these 5 cases survived after esophagectomy. However, in the case reported by Nezu et al. [8], the tumor was confined to the esophageal submucosa and was associated with no lymph node metastases. This patient survived for 7 years with no evidence of tumor recurrence after esophagectomy [8].

The histogenesis of the signet-ring cell component remains unclear. Takubo et al. [6] have reported, based on their immunohistochemical and ultrastructural findings, that the signet-ring cells had an intermediate form of squamous and adenocarcinoma cells. They suggested the esophageal mucosal epithelium as a possible origin for signet-ring cell carcinoma of the esophagus [6]. Conversely, Kuwano et al. [9] have suggested that glandular or mucin-secreting components arise in squamous cell carcinoma as a result of field carcinogenesis involving both the covering squamous epithelium and the mucous gland in the esophagus. In these 3 cases, the signet-ring cells were mainly located at the periphery of the deeply invasive parts of the squamous cell carcinomas. These findings suggest that the signet-ring cells developed at a late stage of tumor progression of esophageal squamous cell carcinoma.

Although preoperative chemotherapy or radiotherapy was performed in 2 of the 3 cases reported here, a diffusely infiltrative growth in the subepithelial layers of the esophagus was histologically observed in all of the 3 tumors. These features were most typically seen in case 2, in which almost the entire esophagus was involved by diffuse infiltration of the submucosal signet-ring cell carcinoma. The appearance of subepithelial growth has been described in the case reported by Takubo et al. [6] and in the case reported by Sasajima et al. [7]. Considering the fact that diffuse submucosal extension was commonly observed in cases of signet-ring cell carcinoma of the stomach or colon, it may be that subepithelial spread is a common property of signet-ring cell carcinomas of the digestive tract. Clinically, these characteristics of tumor growth of esophageal signet-ring cell carcinoma imply some difficulty for making a diagnosis of this tumor by endoscopic biopsy.

In conclusion, signet-ring cell carcinomas rarely develop as a mixture of squamous cell carcinoma in the esophagus. Our results and those previously reported suggest that most of these tumors are aggressive neoplasms and are associated with a poor prognosis after esophageal resection.

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